IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of

Applicant(s)	:	Catherine M. Verfaillie et al.
Application No.	:	10/561,826
Filed	:	October 17, 2006
Title	:	Neuronal Differentiation of Stem Cells
Examiner	:	Chang Yu Wang
Art Unit	:	1649
Attorney Docket	:	890003-2006.1

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

Listed on accompanying Forms PTO/SB/08a and PTO/SB/08b are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98.

Applicants would like to bring to the Examiner's attention the following related applications in the above-identified patent application:

Application/ Publication. No.	Filing/Pub. Date	Attorney Docket	Title
20040107453	2006-06-03	890003-2001	Multipotent Adult Stem Cells, Sources Thereof, Methods of Obtaining Same, Methods of Differentiation Thereof, Methods of Use Thereof and Cells Derived Thereof
20060030041	2006-02-09	890003-2000.1	Multipotent Adult Stems Cells and Methods for Isolation

Application/ Publication. No.	Filing/Pub. Date	Attorney Docket	Title
20050283844	2005-12-22	704675-2001	Multipotent Adult Stem Cells, Sources Thereof, Methods of Obtaining Same, Methods of Differentiation Thereof, Methods of Use Thereof and Cells Derived Thereof
20050181502	2005-08-18	704676-2001	Multipotent Adult Stem Cells and Methods for Isolation
20060228798	2006-10-12	890003-2003.1	Homologous Recombination in Multipotent Adult Progenitor Cells
20070128171	2007-06-07	890003-2008.1	Tissue-Engineered Blood Vessels
10/945,528	2004-09-20	2017.002US1	MAPC Generation of Muscle Tissue
20070009500	2007-01-11	2017.004US1	Compositions and Methods for the Treatment of Lysosomal Storage Disorders
20080031820	2008-02-07	2017.006US1	Swine Multipotent Adult Progenitor Cells
20060008450	2006-01-12	2017.008US2	Use of Multipotent Adult Stem Cells in the Treatment of Myocardial Infarction and Congestive Heart Failure
11/884,098	2006-02-10	2017.010US1	Vascular/Lymphatic Endothelial Cells
11/919,901	2007-11-05	2017.011US1	Use of NK Inhibition to Facilitate Persistence of MHC-I Negative Cells
11/587,511	2006-10-23	2017.012US1	MAPC Generation of Lung Tissue
11/919,899	2007-11-05	2017.013US1	Use of MAPC or Progeny Therefrom to Populate Lymphohematopoietic Tissues
20080194024	2008-08-14	2017.014US1	Culture of Non-Embryonic Stem Cells at High Cell Density
20080194021	2008-08-14	2017.015US1	Use of GSK3 Beta Inhibitor to Maintain Pluripotency of Cultured Non-Embryonic Stem Cells
12/089,868	2008-04-10	2017.016US1	Differentiation of Non-Embryonic Stem Cells to Cells Having a Pancreatic Phenotype
PCT/US07/024415	2007-11-26	2017.017WO1	Endodermal Progenitor Cells

Application/ Publication. No.	Filing/Pub. Date	Attorney Docket	Title
20060177925	2006-08-10	2017.018US1	Kidney Derived Stem Cells and Methods for Their Isolation, Differentiation and Use
20060263337	2006-11-23	ATHS0019US1	Immunomodulatory Properties of MAPC and Uses Thereof
12/093,159	Unknown	ATHS0019US2	Immunomodulatory Properties of MAPC and Uses Thereof
11/808,933	2007-06-13	ATHS0024US1	High Oct3/4 MAPCs and Methods Therefore

Continuations and divisions may be later filed on the cases listed above, or cited to the Examiner in any previous Communication Concerning Related Applications. Applicants request that the Examiner review all continuation and divisionals of the above-listed or previously-listed patent applications before allowing the claims of the present application.

Applicants would also like to bring to the Examiner's attention the following discussion regarding several references in Applicants' PTO/SB/08b.

Nature/Experimental Hematology FACS Analysis Applicants' Form PTO/SB/08b cites an article by the *New Scientist* (an on-line scientific trade journal providing layperson analysis of scientific findings in peer-reviewed journals) published on February 15, 2007. See Aldous P, Reich ES., "Flawed stem cell data withdrawn', *New Scientist* in Applicants' Form PTO/SB/08b. In that article Peter Aldhous, San Francisco Bureau Chief, discussed results reported in two papers from Dr. Verfaillie's laboratory group. See Jiang et al., *Exp. Hematol.*; 30:896-904 (2002) and Jiang et al., *Nature*; 418:41-49 (2002) in Applicants' Form PTO/SB/08b. In this article, Aldhous discloses errors relating to the reporting of flow cytometry results and implies the technology platform is flawed. Two questions were raised.

Is there a duplication of FACS plots in Figure 1 of the *Nature* paper and Figure 2 of the *Experimental Hematology* paper?

In the FACS plots in Figure 1 of the *Nature* paper, the control IgG staining for different specific antibodies was not identical even though the IgG subtype was the same. Should the control stain pattern should be more similar than what was reported?

Point One

There is indeed duplication. Dr. Verfaillie concluded this likely occurred because both papers were under review at the same time and came out in press within a few weeks of one another. Dr. Verfaillie alerted the University of Minnesota through standard internal channels and requested an objective review. Accordingly, the University convened a formal inquiry by a panel of internal and external experts. The panel reviewed extensive evidence and formally met at the University August 10-11, 2006. Based on the findings of the inquiry panel, the University concluded that there was not sufficient evidence of academic misconduct to warrant any further investigation. The panel also concluded that the explanation of honest error was more believable than deliberate falsification. On October 11, 2006, *New Scientist* was advised by the University of the results of the University's investigation. In February 2007, *New Scientist* published the article.

Point Two

The second observation relates to the control staining routinely performed in flow cytometry. The "isotype control" is a negative control applied to a sample, in which the same isotype class of antibody (IgM, IgG1, IgG2 etc.) is used in place of the antigen specific antibody. This control antibody does not react to mouse antigens. The control antibody is used to determine any non-antigen specific staining in the analysis. The determination of positive or negative staining is based on the staining comparison of the test antibody to the isotype control.

The data in the figures show inconsistency in the background staining seen with the isotype control. That is, one would expect duplicate signals in repeating the isotype control for each marker, and in fact there is

variability in the negative threshold. This variability might be due to different machine sensitivity settings used on different days – this is operator controlled. This does not change the relative positive or negative findings when comparing the test antibody to isotype control, and these data are consistent with the multiple analyses performed by the Verfaillie lab over the years.

On this issue, the inquiry panel (FACS experts) above suggested that stem cell experts be consulted on the question of whether the differences in IgG control stains would affect the conclusion of the papers. The University then requested opinions of three independent stem cell scientists. Two responded (the third failed to respond by the extended deadline). The conclusions were not in perfect agreement so the University suggested that Dr. Verfaillie send letters to the two journals and let the scientific community decide the issue. Dr. Verfaillie then submitted letters of explanation to the respective Editors notifying them of the errors and requesting that Errata be published to advise the scientific community. *Experimental Hematology* accepted the explanation and did not pursue the matter further. *Nature*, however, conducted its own review and convened a peer-reviewed panel. This panel of experts concluded that "although the figure data were flawed, the paper's conclusions are still valid." See Check, E., "Stem-cell paper corrected" *Nature*; 447:763 (2007) in Applicants' Form PTO/SB/08b.

In addition, a new figure was inserted with data that do not have the flaw in the IgG control staining pattern. The new phenotype, without problems with the control stains, indicates that MAPCs have the identical phenotype as was shown in the original phenotype.

Blood Western Blots

New Scientist continued to scrutinize Dr. Verfaillie's publications and on March 24, 2007 ultimately published a report (See Aldous P, Reich ES., "Fresh questions on stem cell findings" *New Scientist* in Applicants' Form PTO/SB/08b) of an error in a third publication from Dr. Verfaillie's laboratory. See Reyes et al., *Blood*; 98:2615-25 (2001) in Applicants' Form PTO/SB/08b. Specifically, Reyes et al.

reported differentiation of MAPC (then labeled "mesenchymal progenitor cells") into cells expressing osteoblast (collagen, osteopontin, and bone sialoprotein) and chondroblast (collagen I and collagen II) markers. Figure 5A shows an actin control for the bone sialoprotein blot. Figure 6B shows a blot labeled as collagen II. But the blot is the same as the actin blot in Figure 5A in opposite orientation. This is clearly an error.

In fact, a review of Western blots in the original laboratory experiments from Dr. Reyes uncovered the Figure 5A blot for actin. There also was a collagen II blot. But that blot was not shown in Figure 6B. It appears that when Figure 6B was put together, a reversed actin blot was inadvertently used instead of the existing actual collagen II blot. For the sake of precision, please note that the blots that were uncovered were not the exact exposures that were sent to *Blood* (discussed below), but were identified as a different exposure of the same blot.

Patent Application Western Blots

Finally, there were three Western blot figures in Verfaillie's U.S. patent application 10/048,757 in which the descriptive text was correct and the actual blots existed, but where the actual blots were not used to make the figures. (1) The patent application states that MAPCs differentiate into cells expressing collagen II and refers to Figure 6. See pages 17, 30, and 75 of the specification. But Figure 6 itself does not actually show the collagen II blot. The osteonectin blot (Figure 5A, *Blood*) was inadvertently used instead of the existing actual collagen II blot. (2) The patent application states that MAPCs differentiate into cells expressing bone sialoprotein and refers to Figure 6. See pages 17, 30, and 75 of the specification. But Figure 6 itself does not actually show the bone sialoprotein blot. The actin blot (Figure 5A, *Blood*) was inadvertently used instead of the existing actual bone sialoprotein blot. (3) The specification states (pages 19 and 35) that MAPCs express both Tie/Tek and VWF (endothelial markers) and refers to Figure 10 as showing a Western blot for Tie/Tek. But the blot corresponds to the Western blot for VWF instead of the existing actual Tie/Tek blot.

Accordingly, blots for collagen II, bone sialoprotein, and Tie/Tek were, in fact, available. But, through an inadvertent error, those blots were not used to make the figures. The University of Minnesota has convened a new panel to investigate whether there was any misconduct that led to these errors. Again, please note that the three blots (collagen II, bone sialoprotein, and Tie/Tek) were not the exact exposures that were sent to *Blood* (discussed below), but were identified as a different exposure of the same blot.

Drs. Reyes and Verfaillie believe that the erroneous blots in the figures were not the result of deliberate error. In fact, it is not reasonable to believe that the inventors acted deliberately and it is reasonable to believe that the errors were unintentional. That is because it is unreasonable to believe that the inventors would deliberately substitute an incorrect blot when they already had done the experiments and had the correct blots (collagen II, Tie, and bone sialoprotein) on hand. The University has also provided to *Blood* extensive documentation of relevant data from original laboratory notebooks, certifying that the materials represent true and correct copies of original data.

Effect on Patent Application

With respect to any patent applications related to this subject matter, Applicants submit that the errors do not detract from the patentability of any inventions disclosed therein. First, the verbal disclosure in the PCT application is correct. All statements about expression of the three markers are factually correct and reflect the inventors' actual data. In addition to the statements about the markers, there were other figures (not Western blots) showing expression of all of the markers. The erroneous figures were added when the PCT application was prepared. These figures were not in the two priority provisional applications. But in those two priority applications, expression of collagen II, bone sialoprotein, and Tie had already been shown. Therefore, the later-filed erroneous figures were duplicative for the earlier-filed differentiation results.

Second, even if differentiation into cells expressing collagen II, Tie, and bone sialoprotein had never been shown, this would not affect the ultimate conclusion, which is that MAPC form cells with chondroblast, endothelial, and osteoblast markers. In the PCT patent application, Tie was not the only evidence of endothelial differentiation. Collagen II was not the only evidence of chondroblast differentiation. And bone sialoprotein was not the only evidence of osteoblast differentiation. Thus, even if none of these markers had been assayed or reported, the person of ordinary skill in the art still would have been taught that MAPC could form cells with chondroblast, endothelial, and osteoblast phenotype.

Third, with respect to the instant application in particular, none of the claims explicitly recites or relies on any of the markers at issue. Therefore, even if differentiation into cells expressing collagen II, Tie, and bone sialoprotein had never been shown, the patentability and scope of the claims would not be affected. Claims are directed to MAPC that can form cells with mesodermal phenotypes. The specification shows mesodermal cell types in addition to chondroblast, endothelial, and osteoblast. So even if no chondroblast, endothelial, or osteoblast cell differentiation had been done or reported, the person of ordinary skill still would have believed that MAPC could differentiate mesodermal cell types. Thus, Applicants believe that the errors would not have detracted from adequate written description.

With respect to enablement, the errors would not have interfered with the ability of the person of ordinary skill in the art to make and use the MAPC. The specification states that the MAPC form the cell types at issue. The fact that the blot was technically a different protein would not have even been recognized by the person of ordinary skill in the art who made or used MAPC according to the specification. Accordingly, Applicants believe that the errors would not have detracted from the ability of the person of ordinary skill in the art to make and use the MAPC.

Also of potential interest in this regard are the following references in Applicants' Form PTO/SB/08b: Chi, "Adult stem cell figure retracted" *The Scientist*; (June 13, 2007); Glenn, "Paper on versatility of adult stem cells comes under question" *The Chronicle*; (February 26, 2007); Holden, "Stem Cells.

Controversial marrow cells coming into their own?" *Science*; 315:760-761 (2007); Lerner et al., "Stem cell study was flawed, U panel finds" *Star Tribune*; (February 27, 2007); Noonan, "Limitations on the usefulness of adult stem cells" *Patent Docs*; (February 28, 2007); Pincock, "Adult stem cell report questioned" *The Scientist*; (February 26, 2007); Serafini et al., "Hematopoietic reconstitution by multipotent adult progenitor cells: precursors to long-term hematopoietic stem cells" *J. Exp. Med.*; 204:129-39 (2007); Verfaillie, "Letter to the Editor" *Experimental Hematology*; (2007); and Jiang et al., "Pluripotency of mesenchymal stem cells derived from adult marrow, Supplemental Information for Verfaillie Corrigendum" *Nature*; 418:41-49 (2002).

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that an exhaustive search has been made, or that there does not exist information more material to the examination of the present patent application. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will review art of record in all 35 U.S.C. § 120 priority documents.

This Information Disclosure Statement is filed more than three months after the U.S. filing date, and after the mailing date of the first Office Action, but before the mailing date of a Final Office Action or Notice of Allowance (37 C.F.R. 1.97(c)).

Applicants submit herewith twelve (12) Foreign Patent Documents and forty-one (41) Non-Patent Literature Documents.

Applicants believe that a fee of $180 is due with this submission. Payment of such fee is being made simultaneously with this filing via Electronic Funds Transfer. The Director is hereby authorized to charge any deficiency, or credit any overpayment, to our Deposit Account No. 20-0809.

Respectfully submitted,

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